Published in final edited form as:

J Pediatr. 2012 June ; 160(6): 978–983. doi:10.1016/j.jpeds.2011.12.006.

Cancer in Children with Nonchromosomal Birth Defects

Paul Graham Fisher, MD[1,2,3,4], **Peggy Reynolds, PhD**[5,6], **Julie Von Behren, MPH**[6], **Suzan L. Carmichael, PhD**[2], **Sonja A. Rasmussen, MD**[7], and **Gary M. Shaw, DrPH**[2]

[1]Department of Neurology, Stanford University, Palo Alto

[2]Department of Pediatrics, Stanford University, Palo Alto

[3]Department of Neurosurgery, Stanford University, Palo Alto

[4]Department of Human Biology, Stanford University, Palo Alto

[5]Department of Health Research and Policy, Stanford University, Palo Alto

[6]Cancer Prevention Institute of California, Berkeley, CA

[7]Centers for Disease Control and Prevention, Atlanta, GA

Abstract

Objective—To examine whether the incidence of childhood cancer is elevated in children with birth defects but no chromosomal anomalies.

Study design—We examined cancer risk in a population-based cohort of children with and without major birth defects born between 1988 and 2004, by linking data from the California Birth Defects Monitoring Program, the California Cancer Registry, and birth certificates. Cox proportional hazards models generated hazard ratios (HRs) and 95% Cls based on person-years at risk. We compared the risk of childhood cancer in infants born with and without specific types of birth defects, excluding infants with chromosomal anomalies.

Results—Of the 4869 children in the birth cohort with cancer, 222 had a major birth defect. Although the expected elevation in cancer risk was observed in children with chromosomal birth defects (HR, 12.44; 95% Cl, 10.10-15.32), especially for the leukemias (HR, 28.99; 95% Cl, 23.07-36.42), children with nonchromosomal birth defects also had an increased risk of cancer(HR, 1.58;95% Cl, 1.33-1.87), but instead for brain tumors, lymphomas, neuroblastoma, and germ cell tumors.

Conclusion—Children with nonchromosomal birth defects are at increased risk for solid tumors, but not leukemias. Dysregulation of early human development likely plays an important role in the etiology of childhood cancer.

The etiology of childhood cancer is largely unknown. Less than 5% of childhood cancers are directly attributable to a genetic syndrome, and the vast majority of these are leukemias in children with Down syndrome, bilateral retinoblastoma, tumors with neurofibromatosis, or

Reprint requests: Paul Graham Fisher, MD, Stanford University Medical Center, 750 Welch Road, Suite 317, Palo Alto, CA 94304-1510. pfisher@stanford.edu.

The authors declare no conflicts of interest.

hereditary Wilms tumor.[1] How many other childhood cancers may be related to genetic alterations not readily linked to a syndrome or chromosomal anomaly remains unknown. Likewise, the roles that environmental exposures, gene-environment interactions, and epigenetic factors play in pediatric cancer have not been clearly established. Despite advances in molecular medicine, our understanding of the causes of childhood cancer remains incomplete.

Previous investigators have examined the relationship between childhood cancer and birth defects in population-based datasets. [2-8] These studies pointed toward a connection between birth defects and childhood cancer, in particular an association between trisomy 21 and leukemia. Consequently, we undertook the largest population-based North American effort to date to examine whether the incidence of childhood cancer is elevated in children with structural birth defects, specifically birth defects not associated with chromosomal anomalies.

Methods

We linked 3 data sources: the California Birth Defects Monitoring Program (CBDMP) registry, the California Cancer Registry (CCR), and the live birth and death files from the California State Office of Vital Records. This study included 3 221 849 live births recorded between 1988 and 2004 in California counties covered by the CBDMP registry.

Data on birth defects were drawn from cases ascertained through the CBDMP's surveillance program, a population-based active surveillance system for collecting information on births with major congenital malformations in California counties. (Cases with only minor anomalies are not identified in the registry.) Diagnostic and demographic data (including information on chromosomal anomalies) were collected by program staff from multiple sources of medical records for all liveborn and stillborn (defined as a fetus ≥20 weeks' gestational age) infants.[9] Most structural birth defects diagnosed within 1 year of delivery are ascertained; overall ascertainment has been estimated as 97% complete.[10]

Since 1988, the CCR has maintained a legislatively mandated population-based surveillance system for all newly diagnosed cancers, excluding basal and squamous cell carcinomas of the skin, among all California residents, and quality control studies indicate 99% ascertainment.[11] Routinely collected CCR data include detailed case demographic, diagnostic, and treatment characteristics. The CCR follows a rigorous, active surveillance protocol modeled after the National Cancer Institute's Surveillance, Epidemiology and End Results program. The present study includes information on cancer cases diagnosed between 1988 and 2006 in children aged <15 years.

Using probabilistic record linkage (LinkPlus), we linked children in the cancer file to California live birth certificates (birth years 1988-2004). The personal identifiers common to both databases and used for linkage were name, date of birth, sex, and race/ethnicity. Birth defects cases are routinely linked to vital statistics records by the CBDMP, using probabilistic record linkage and personal identifiers common to both databases (eg, name, date of birth). Reasons for lack of matching to vital records include adoption and, for the

cancer cases, birth outside of California. We subsequently matched those cancer cases for which we identified a birth certificate to the birth defects registry by a unique numeric identifier available from the Office of Vital Records. We also linked all of the births to the state death files to identify any children who died, and censored these children at date of death (linked by name, date of birth, and sex).

Each potential case with a link to both the birth defects registry and to the cancer registry was reviewed by a clinical geneticist (S.R.) to determine whether each case had only a minor birth defect (eg, polydactyly, branchial cleft cyst) or a defect secondary to the tumor (eg, hydronephrosis secondary to a kidney tumor, hydrocephalus associated with a brain tumor). Infants with either of these conditions were excluded from the total cohort considered to have both a birth defect and cancer.

We compared the risk of cancer in the 2 cohorts (those born with major birth defects and those born without major birth defects between 1988 and 2004) using Cox proportional hazards models to generate hazard ratios (HRs) and 95% CIs, based on person-years at risk. We censored each individual at time of cancer diagnosis, death, end of study period, or age 15 years. We analyzed the risk for all cancers combined, as well as for major subtypes, such as leukemia, neuroblastoma, and central nervous system (CNS) tumors, and some specific cancers, including acute lymphoblastic leukemia, acute myelogenous leukemia, and non-CNS germ cell tumors. We classified the cancers in accordance with the International Classification of Childhood Cancer, Third Edition; however, we included intracranial and intraspinal germ cell tumors with the CNS tumors and excluded renal carcinomas from Wilms tumors (nephroblastomas).

We examined all birth defects combined and groupings of birth defects defined based on British Pediatric Association Classification of Diseases codes, as modified by the Centers for Disease Control and Prevention (http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf), a classification scheme similar to the International Classification of Diseases. The 3-digit codes reflect broad birth defect groupings. Because the overall results were likely to be driven by the well-known association between Down syndrome and leukemia, we examined risks in children with and without chromosomal anomalies separately, and we excluded children diagnosed with leukemias from our analysis of the overall risk of cancer in children with birth defects but no chromosomal anomalies.

Results

We identified a birth cohort of 3 221 849 live births for the period 1988-2004, coinciding with the study population in which surveillance for birth defects was conducted. In this cohort, the CBDMP identified a total of 65 585 infants with structural birth defects (2%). The phenotypes of these infants are displayed in **Table I** by birth defect category. The categories are not mutually exclusive, because many infants had multiple defects.

We identified 4869 children with cancer in the birth cohort, representing 81.5% of all cancers occurring in children living in the study counties during the study period (ie, 81.5% were linked to birth certificates). The distribution of cancer types in these children is shown

in **Table I**. A total of 270 children were included in the CBDMP registry as well. Of these 270, 48 were excluded after detailed case review for having a defect considered minor or likely secondary to the cancer, leaving 222 infants with both major birth defects and cancer. In these 222 infants, the most common cancers were leukemias and CNS tumors.

Table II lists cancer risks in the 6327 children with chromosomal anomalies, including 3923 with Down syndrome. As expected, the risk for leukemia was highly elevated (HR, 28.99; 95% CI, 23.07-36.42). The HR for acute myelogenous leukemia was much higher than that for acute lymphoblastic leukemia. These children also had an increased risk of Wilms tumor (HR, 13.43; 95% CI, 5.54-32.55).

Table II also shows the risks of specific types of childhood cancer in infants born with birth defects but without chromosomal anomalies. In contrast to children with chromosomal anomalies, this group was not at increased risk for leukemia (HR, 0.96; 95% CI, 0.66-1.38). However, they were at increased risk for the other types of cancer examined, namely solid tumors including lymphomas, CNS tumors, neuroblastomas, and non-CNS germ cell tumors.

Demographic characteristics for the children born without chromosomal anomalies, comparing children with and without birth defects and with and without cancer, are shown in **Table III**. The 4 groups demonstrated no significant differences in terms of sex, birth year, or race/ethnicity. The mothers of infants with birth defects and cancer tended to be older and more educated than the mothers of the other groups of children.

The risk of childhood cancer in children with specific types of birth defects, excluding children with chromosomal anomalies or leukemias, is delineated in **Table IV**. Infants diagnosed with any of the birth defect phenotypes except cleft lip or palate had a ≥2-fold greater risk of developing cancer during childhood.

Further analyses to investigate the specific cancer phenotype in children who were previously diagnosed with birth defects were hindered by small sample sizes (data not shown), and thus we cannot firmly infer specific birth defect and specific cancer associations. We can make some tentative observations, however, including that in children born with “other congenital anomalies of the nervous system” (British Pediatric Association Classification of Diseases [BPA] 742), CNS tumors were most common (occurring in 47% of the cases with BPA 742 and cancer), and that in children born with “other congenital anomalies of the heart” (BPA 746), lymphomas were most common (38%).

Discussion

To identify new potential etiologic clues underlying birth defects and childhood cancers, we undertook a large population-based North American study to examine whether the incidence of childhood cancer was elevated in children with structural birth defects. Our findings confirm previous observations that children born with chromosomal abnormalities are at increased risk for developing cancer in childhood, as demonstrated by, for instance, the known association between Down syndrome and leukemia.

Our findings extend the knowledge base beyond these previous observations, however. We found that children with nonchromosomal birth defects had an elevated risk of cancer (HR, 1.58; 95% CI, 1.33-1.87), particularly for CNS tumors, lymphomas, neuroblastomas, and germ cell tumors, but not for leukemia. Furthermore, we observed that risk of developing cancer in childhood was substantially increased (2- to 3- fold) in children with nearly every structural birth defect phenotype, with the exception of cleft lip or palate. More specifically, and more tentatively, we found that CNS tumors were more common in children with a history of CNS birth defects and that lymphomas were more common in children with a history of congenital heart defects.

Previous investigations examined the relationship between childhood cancer and birth defects in population-based datasets,[2-8] but did not take our approach to exclude chromosomal defects. These studies varied in their definition of what constituted a birth defect, but all reported an increased risk of cancer in children with birth defects. A Canadian study comparing cohorts of children with and without birth defects found a 2-fold higher risk of all types of cancer, particularly leukemia, CNS tumors, and sympathetic nervous system tumors, in the children with birth defects.[2] They also found a 6-fold greater risk of cancer in the first year of life in the children with birth defects. The 2 population-based cohort studies conducted in the United States were based on relatively small cohorts of children with birth defects (approximately 19 000 in one study and 10 000 in the other).[4,5] The largest study to date addressing this issue was published by researchers in Norway and Sweden.[3] These researchers linked data on more than 5 million births to cancer registries in the 2 countries to evaluate cancer risks in individuals with birth defects. They computed standardized incidence ratios and found that children with birth defects had an overall increased risk of 1.7, with especially high risks associated with Down syndrome and nervous system malformations. Notably, although most of the population-based studies to date conducted analyses or subanalyses excluding children with Down syndrome, none systematically evaluated cancer risks in children without chromosomal anomalies as was done in the present study.

Several previous case-control studies based on interview data also have examined cancer risk in children with birth defects. Four of these studies reported increased risks for cancer, generally in the 2-fold range, in children with birth defects.[12-15] Similar to our results, 2 studies of leukemia that excluded Down syndrome found no overall difference in the risk of birth defects between leukemia cases and controls.[16,17] Hospital-based clinical studies also have noted a high prevalence of morphological abnormalities in children with cancer.[18-20]

All of the previous studies were conducted in primarily non-Hispanic white children in northern Europe, Canada, Australia, and the United States. The cohort of California births included in the present study was racially and ethnically diverse: 56% Hispanic, 25% non-Hispanic white, 10% Asian, and 7% non-Hispanic black. Interestingly, our results are consistent with those of the previous studies in predominantly non-Hispanic white populations.

An important strength of the present study is that data on birth defect diagnoses were obtained by active abstraction of diagnostic data from hospital reports and medical records

through the first year of life. This approach ensures relatively complete ascertainment in the study population.[9] Previous studies of birth defects and childhood cancer tended to be limited by passive ascertainment and/or ascertainment only during the newborn period.[2,3] A limitation of the present study is that birth defect diagnoses were limited to relatively broad groupings based on British Pediatric Association Classification of Diseases codes, thereby restricting our ability to interrogate specific birth defects.

Despite our opportunity to evaluate cancer and birth defects in a large and well-characterized population-based sample, the co-occurrence of these outcomes is rare, and our focus was on even rarer nonchromosomal defects. Small sample size is a study limitation that hindered our ability to make more narrow inquiries into specific birth defect–cancer phenotype associations, and thus these connections cannot be firmly inferred. In addition, our ability to examine potential explanatory variables in more depth was limited. However, we note that our results were not substantially different after adjustment for maternal age (data not shown). We chose not to adjust for birth weight, because it might be influenced by the presence of birth defects and/or act as a mediator between birth defect–cancer associations. Differential outmigration from California based on birth defect status could affect our risk estimates; data to address this potential bias were not available.

Etiologies for structural birth defects and childhood cancers remain elusive. Improved clue-finding strategies are needed to unravel these etiologies. The present study takes a first step toward identifying new potential etiologic clues underlying birth defects and childhood cancers by studying the co-occurrence of the 2 broad phenotypes. We found significant co-occurrence of various solid tumors, but not leukemias, with nonchromosomal birth defects. Because teratogenesis and some forms of carcinogenesis represent errors in early growth, the 2 mechanisms likely share biologic underpinnings.[21] Indeed, we hypothesize that dysregulation in human development plays an important role in the etiology of childhood cancer, especially solid tumors. For example, defects in specific homeobox genes might be related to some solid tumors and birth defects, and some CNS tumors have been linked to the *Shh* pathway, a key in regulation of brain development.[22] In contrast, leukemia might hinge on a single gene defect in clonal proliferation of leukocytes and be less closely related to aberrant developmental pathways.

Continued inquiries into the predisposition to cancer in young children with structural birth defects should help elucidate etiologic commonalities between these 2 outcomes. Indeed, molecular tools are available to examine multiple genes simultaneously in children, and the next logical step is to explore the genomic profiles of those children with cancer with and without birth defects. For now, the identification of structural birth defects in the first year of life that indicate possible unrecognized tumor predisposition should serve to alert the pediatrician to a child at increased risk for cancer and contribute significantly to our understanding of the causes of childhood cancer.

Acknowledgments

We thank the California Department of Public Health, Maternal, Child, and Adolescent Health Division; Office of Vital Records; and California Cancer Registry for providing data for these analyses. We also thank Michael

Layefsky for his work on the record linkage portions of this project, and Dr Martha Linet for serving as an external advisor.

Supported by the Association of American Medical Colleges and the Centers for Disease Control and Prevention (grant MM-1125-09/09, under Cooperative Agreement U36/CCU319276 CFDA 93.283), and partially supported by Centers for Disease Control and Prevention grant CDC 6U01DD000489. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the California Department of Public Health or the Centers for Disease Control and Prevention.

Glossary

BPA	British Pediatric Association Classification of Diseases
CBDMP	California Birth Defects Monitoring Program
CCR	California Cancer Registry
CNS	Central nervous system
HR	Hazard ratio

References

1. Narod SA, Stiller C, Lenoir GM. An estimate of the heritable fraction of childhood cancer. Br J Cancer. 1991; 63:993–9. [PubMed: 2069856]
2. Agha MM, Williams JI, Marrett L, To T, Zipursky A, Dodds L. Congenital abnormalities and childhood cancer. Cancer. 2005; 103:1939–48. [PubMed: 15770693]
3. Bjorge T, Cnattingius S, Lie RT, Tretli S, Engeland A. Cancer risk in children with birth defects and in their families: a population-based cohort study of 5.2 million children from Norway and Sweden. Cancer Epidemiol Biomarkers Prev. 2008; 17:500–6. [PubMed: 18296646]
4. Mili F, Khoury MJMJ, Flanders WD, Greenberg RS. Risk of childhood cancer for infants with birth defects, I: a record-linkage study, Atlanta, Georgia, 1968-1988. Am J Epidemiol. 1993; 137:629–38. [PubMed: 8470664]
5. Mili F, Lynch CF, Khoury MJ, Flanders WD, Edmonds LD. Risk of childhood cancer for infants with birth defects, II: a record-linkage study, Iowa, 1983-1989. Am J Epidemiol. 1993; 137:639–44. [PubMed: 8470665]
6. Rankin J, Silf KA, Pearce MS, Parker L, Ward Platt M. Congenital anomaly and childhood cancer: a population-based, record linkage study. Pediatr Blood Cancer. 2008; 51:608–12. [PubMed: 18623214]
7. Windham GC, Bjerkedal T, Langmark F. A population-based study of cancer incidence in twins and in children with congenital malformations or low birth weight, Norway, 1967-1980. AmJ Epidemiol. 1985; 121:49–56. [PubMed: 3155484]
8. Altmann AE, Halliday JL, Giles GG. Associations between congenital malformations and childhood cancer: a register-based case control-study. Br J Cancer. 1998; 78:1244–9. [PubMed: 9820188]
9. Croen LA, Shaw GM, Jensvold NG, Harris JA. Birth defects monitoring in California: a resource for epidemiological research. Paediatr Perinat Epidemiol. 1991; 5:423–7. [PubMed: 1754501]
10. Schulman J, Hahn JA. Quality control of birth defect registry data: a case study. Public Health Rep. 1993; 108:91–8. [PubMed: 8434104]
11. Perkins, CI.; Cohen, R.; Morris, CR.; Allen, M.; Kwong, SL.; Schlag, R., et al. Cancer in California: 1989-1995. California Department of Health Services, Cancer Surveillance Section; Sacramento, CA: 1998.
12. Mertens AC, Wen W, Davies SM, Steinbuch M, Buckley JD, Potter JD, et al. Congenital abnormalities in children with acute leukemia: a report from the Children's Cancer Group. J Pediatr. 1998; 133:617–23. [PubMed: 9821417]

13. Menegaux F, Olshan AF, Reitnauer PJ, Blatt J, Cohn SL. Positive association between congenital anomalies and risk of neuroblastoma. Pediatr Blood Cancer. 2005; 45:649–55. [PubMed: 15547919]
14. Munzer C, Menegaux F, Lacour B, Valteau-Couanet D, Michon J, Coze C, et al. Birth-related characteristics, congenital malformation, maternal reproductive history and neuroblastoma: the ESCALE study (SFCE). Int J Cancer. 2008; 122:2315–21. [PubMed: 18076072]
15. Johnson KJ, Ross JA, Poynter JN, Linabery AM, Robison LL, Shu XO. Paediatric germ cell tumours and congenital abnormalities: a Children's Oncology Group study. Br J Cancer. 2009; 101:518–21. [PubMed: 19603020]
16. Infante-Rivard C, Amre DK. Congenital anomalies in children with acute lymphoblastic leukaemia and in their family. Int J Epidemiol. 2001; 30:350–2. [PubMed: 11369741]
17. Johnson KJ, Roesler MA, Linabery AM, Hilden JM, Davies SM, Ross JA. Infant leukemia and congenital abnormalities: a Children's Oncology Group study. Pediatr Blood Cancer. 2010; 55:95–9. [PubMed: 20486175]
18. Citak FE, Citak EC, Akkaya E, Kosan B, Ezer U, Kurekci AE. Minor anomalies in children with hematological malignancies. Pediatr Blood Cancer. 2011; 56:258–61. [PubMed: 20860040]
19. Merks JH, Ozgen HM, Koster J, Zwinderman AH, Caron HN, Hennekam RC. Prevalence and patterns of morphological abnormalities in patients with childhood cancer. JAMA. 2008; 299:61–9. [PubMed: 18167407]
20. Roganovic J, Radojcic-Badovinac A, Ahel V. Increased prevalence of minor anomalies in children with hematologic malignancies. Med Pediatr Oncol. 2002; 38:128–30. [PubMed: 11813182]
21. O'Brien PJ, Hales BF, Josephy PD, Castonguay A, Yamazoe Y, Guengerich FP. Chemical carcinogenesis, mutagenesis, and teratogenesis. Can J Physiol Pharmacol. 1996; 74:565–71. [PubMed: 8884021]
22. Roussel MF. New concepts in organ site research on medulloblastoma: genetics and genomics. Future Oncol. 2010; 6:1229–31. [PubMed: 20799868]

Table I

Diagnoses of birth defects and childhood cancer in children born in California between 1988 and 2004

Birth defects: BPA3 code and description	Number of liveborn cases*
658 – Amniotic band	509
740 – Anencephalus and similar anomalies	428
741 – Spina bifida	1176
742 – Other congenital anomalies of the nervous system	9199
743 – Congenital anomalies of the eye	11 027
744 – Congenital anomalies of the ear, face and neck	16 262
745 – Bulbus cordis anomalies/cardiac septal cleft	13 280
746 – Other congenital anomalies of the heart	9762
747 – Other congenital anomalies of the circulatory system	8465
748 – Congenital anomalies of the respiratory system	11 203
749 – Cleft palate and cleft lip	5209
750 – Other congenital anomalies of the upper alimentary system	13 369
751 – Other congenital anomalies of the digestive system	6164
752 – Other congenital anomalies of the genital organs	11 016
753 – Other congenital anomalies of the urinary system	6591
754 – Certain congenital musculoskeletal deformities	13 146
755 – Other congenital anomalies of the limbs	15 503
756 – Other congenital musculoskeletal anomalies (excluding 754)	14 031
757 – Congenital anomalies of the integument	16 172
758 – Chromosomal anomalies	6327
759 – Other and unspecified congenital anomalies	3587
Childhood cancers: major diagnostic groups†	**Number of cases‡**
Leukemia	1811
Acute lymphoblastic leukemia	1475
Acute myelogenous leukemia	261
Lymphoma	422
CNS (including germ cell tumors of brain)	1082
Neuroblastoma	317
Wilms tumor (nephroblastoma, excluding renal carcinoma)	249
Non-CNS germ cell tumors	156
Rhabdomyosarcoma	153

*Totals are by diagnosis; that is, some subjects had more than one diagnosis, and thus totals do not sum to 65 585.

†Based on the International Classification of Childhood Cancer, Third Edition.

‡Fifty-eight children had multiple types of cancer. Cases not fitting into major diagnostic groups are not listed in the Table, and thus the total does not add up to 4869.

Table II

. Risks of specific types of childhood cancer among infants born with major birth defects, separately for those with and without chromosomal anomalies

Cancer groups	Children with chromosomal anomalies (n = 6327)		Children without chromosomal anomalies (n = 59 258)	
	Number with birth defects and cancer	HR (95% CI)	Number with birth defects and cancer	HR (95% CI)
All	90*	12.44 (10.10-15.32)	132†	1.58 (1.33-1.87)
Leukemia	77	28.99 (23.07-36.42)	29	0.96 (0.66-1.38)
Acute lymphoblastic leukemia	33	14.95 (10.59-21.11)		
Acute myelogenous leukemia	35	101.22 (70.87-144.57)		
Lymphoma	0	-	17	2.24 (1.38-3.63)
CNS tumors (including germ cell tumors of brain)	3	1.87 (0.60-5.79)	34	1.80 (1.28-2.53)
Neuroblastoma	1	2.08 (0.29-14.82)	15	2.85 (1.69-4.78)
Wilms tumor (nephroblastoma, excluding renal carcinoma)	5	13.43 (5.54-32.55)	6	1.45 (0.65-3.26)
Non-CNS germ cell tumor	1	4.32 (0.60-30.82)	8	2.98 (1.46-6.07)
Rhabdomyosarcoma	0	-	6	2.26 (1.00-5.11)

*Among the 90 cases, specific HRs were not calculated for 3 patients (1 each with hepatoblastoma, fibrosarcoma, and thyroid carcinoma).

†Among the 132 cases, specific HRs were not calculated for 17 patients (4 with retinoblastoma, 4 with hepatoblastoma, 2 with bone tumors, 3 with soft tissue sarcomas, 2 with thyroid carcinoma, and 2 with melanoma).

Table III

. Demographic data for children born without chromosomal anomalies, by cancer and birth defect status

	Both cancer and a birth defect (n = 132)	Cancer and no birth defect (n = 4649)	No cancer and birth defect (n = 59 189)	No cancer and no birth defect (n = 3 151 615)
Sex				
Male	75 (57%)	2529 (54%)	36 238 (61%)	1 604 751 (51%)
Female	57 (43%)	2120 (46%)	22 935 (39%)	1 546 846 (49%)
Birth year				
1988-1990	45 (34%)	1485 (32%)	22 184 (38%)	855 185 (27%)
1991-1995	53 (40%)	2142 (46%)	25 328 (43%)	1 385 115 (44%)
1996-1999	31 (23%)	777 (17%)	8305 (14%)	611 355 (19%)
2000-2004	3 (2%)	245 (5%)	3372 (6%)	299 960 (10%)
Maternal race-ethnicity				
Non-Hispanic white	43 (33%)	1322 (29%)	17 434 (30%)	799 073 (26%)
Hispanic	70 (54%)	2532 (55%)	30 597 (53%)	1 751 259 (57%)
Non-Hispanic black	6 (5%)	294 (6%)	4708 (8%)	219 000 (7%)
Asian/Pacific Islander	11 (8%)	431 (9%)	4945 (9%)	315 551 (10%)
American Indian	0	17 (<1%)	319 (1%)	14 679 (<1%)
Maternal age, years				
<20	8 (6%)	549 (12%)	7562 (13%)	398 222 (13%)
20-24	22 (17%)	1143 (25%)	14 900 (25%)	817 512 (26%)
25-29	47 (36%)	1379 (30%)	16 447 (28%)	892 655 (28%)
30-34	32 (24%)	1028 (22%)	12 894 (22%)	366 464 (12%)
35+	23 (17%)	548 (12%)	7367 (12%)	675 914 (21%)
Maternal education				
<High school graduate	36 (31%)	1447 (35%)	18 977 (38%)	1 068 575 (38%)
High school graduate	25 (21%)	1226 (30%)	15 081 (30%)	833 320 (30%)
Some college	28 (24%)	757 (19%)	9014 (18%)	509 738 (18%)
College graduate	29 (25%)	656 (16%)	6895 (14%)	407 739 (15%)

Table IV

Overall risk of childhood cancer in infants born with specific types of birth defects but without chromosomal anomalies and excluding all subjects diagnosed with leukemias*

Birth defect category (BPA3)	Infants with these birth defects	Infants with these birth defects and cancer	HR (95% CI)
Amniotic bands (658)	488	0	-
Anencephalus (740)	423	0	-
Spina bifida (741)	1124	3	3.19 (1.03-9.89)
Other congenital anomaly of nervous system (742)	7678	35	5.83 (4.18-8.14)
Congenital anomaly of eye (743)	6392	24	4.90 (3.28-7.32)
Congenital anomaly of ear, face, neck (744)	11 025	26	2.94 (2.00-4.33)
Bulbus cordis anomaly/cardiac septal closure (745)	10 151	25	3.36 (2.27-4.98)
Other congenital anomaly of heart (746)	7990	23	3.99 (2.65-6.01)
Other congenital anomaly of circulatory system (747)	6840	21	4.28 (2.79-6.57)
Congenital anomaly of respiratory system (748)	7958	24	4.25 (2.85-6.35)
Cleft palate and cleft lip (749)	4662	5	1.25 (0.52-3.02)
Other congenital anomaly of upper alimentary (750)	10 608	23	2.45 (1.62-3.69)
Other congenital anomaly of digestive system (751)	5419	11	2.44 (1.35-4.40)
Congenital anomaly of genital organs (752)	9522	22	2.62 (1.72-3.98)
Congenital anomaly of urinary system (753)	5989	15	3.15 (1.90-5.23)
Certain congenital musculoskeletal deformities (754)	10 263	23	2.56 (1.70-3.86)
Other congenital anomaly of limbs (755)	11 329	23	2.37 (1.57-3.57)
Other congenital musculoskeletal anomaly (756, excluding 754)	11 168	30	3.37 (2.35-4.83)
Congenital anomaly of integument (757)	11 444	31	3.09 (2.17-4.40)
Other and unspecified congenital anomaly (759)	3161	15	7.80 (4.70-12.94)

* Including 103 cases with birth defects and cancer.